Clinical Alert: Low Dose Warfarin Prevents Recurrence of Blood Clots — NHLBI Stops Study

National Heart, Lung, and Blood Institute (NHLBI)
February 24, 2003

A study of long-term, low-dose warfarin to prevent the recurrence of the blood clotting disorders deep vein thrombosis (DVT) and pulmonary embolism resulted in such a high degree of benefit to the patients — without significant adverse effects — that the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health has stopped the study early.

The multi-center Prevention of Recurrent Venous Thromboembolism (PREVENT) trial found a 64 percent reduction in episodes of DVT and pulmonary embolism in study participants taking low-dose warfarin compared to those taking a placebo. Furthermore, there was no evidence of significant risks such as major hemorrhage or other potential side effects of warfarin, which is an anticoagulant — a drug that prevents blood clotting.

At the time the study was terminated, patients had been followed for up to about 4 years with an average of about 2 years. All study participants had experienced a previous episode of either DVT or PE placing them at greater risk of a recurrence.

PREVENT is the first study to evaluate the use of low dose warfarin for the long-term prevention of venous thromboembolism (VTE), a term that includes both DVT and pulmonary embolism. The study will be published in the April 10, 2003 issue of *The New England Journal of Medicine* (*NEJM*). Due to its importance, the *NEJM* posted the article online on February 24.

The trial, which began in 1998, was scheduled to run until 2005. However, at a regularly scheduled meeting of the study's independent Data and Safety Monitoring Board (DSMB) held December 4, 2002, the interim findings were reviewed and based on the strong benefit of low-dose warfarin, the DSMB recommended halting the study. The recommendation was approved by the NHLBI.

"This is an important finding for the estimated half million Americans who each year experience either deep vein thrombosis or pulmonary embolism," said NHLBI Director Claude Lenfant, M.D. "These results suggest that low dose warfarin is a safe and effective way to prevent future episodes of these potentially serious blood clotting problems," added Lenfant.

The current standard treatment for DVT and pulmonary embolism not associated with surgery or another specific cause is 5 to 10 days of intravenous or subcutaneous heparin followed by 3 to 6 months of full-dose warfarin. Therapy typically stops after the initial treatment period because long-term use of full-dose warfarin is associated with a substantial risk of major bleeding. After the initial therapy is completed, recurrent blood clots occur in 6 to 9 percent of patients each year. The new data demonstrate that these recurrent blood clots can be avoided using an inexpensive and safe therapy.

"This is a win-win situation for our patients and for health care providers," said Paul Ridker, M.D., the principal investigator of PREVENT and professor of medicine at Harvard and director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital in Boston.

"The PREVENT results strongly suggest that long-term use of low-intensity warfarin should be considered a new standard of care for the management of venous thrombosis after stopping full-dose warfarin therapy," Ridker added.

In deep vein thrombosis, a blood clot develops in one of the deep veins that is surrounded by muscle near the center of the leg. The clot may partially or completely block blood flow through the vein. Symptoms include pain, sudden swelling in the leg, enlargement of the superficial veins, reddish-blue discoloration of the skin, and warm skin.

If DVT is not treated, it can lead to pulmonary embolism in which the clots detach and travel through the bloodstream to the lungs, where they may enter a pulmonary artery. Large clots that completely block the pulmonary artery can be fatal. Symptoms of pulmonary embolism include sudden shortness of breath, sharp chest pain, a cough with bloody sputum, excessive sweating, rapid pulse, and lightheadedness. Acute DVT can also lead to complications like chronic venous insufficiency, which is characterized by pooling of blood, chronic leg swelling, and increased pressure on the skin.

There are a number of risk factors for DVT and pulmonary embolism, including long periods of inactivity which decrease blood flow. People who are immobile after surgery or serious injuries and travelers on long trips are at increased risk of blood clots.

In addition, the hormone estrogen found in birth control pills has been shown to increase the risk of blood clots. The results of the Women's Health Initiative study, reported last July, found significant increases in pulmonary embolism in healthy women taking combined estrogen and progestin.

Since the start of the PREVENT trial, 508 patients at 52 clinical sites in the US, Canada, and Switzerland were enrolled in the study. Had the study continued, 750 patients would have been enrolled. Participants in PREVENT were age 30 and older and had documented DVT or pulmonary embolism within the previous two years with at least three uninterrupted months of treatment with full-dose warfarin. The patients' episodes of DVT or pulmonary embolism were required to be "idiopathic" — unrelated to recent surgery, trauma, or a diagnosis of metastatic cancer.

Patients in PREVENT were randomly assigned to low-dose warfarin or to placebo and as a "double-blind" study neither the patients nor the investigators knew the treatment assignment.

Of the 253 patients assigned to placebo, 37 had a recurrent episode of DVT or pulmonary embolism compared to 14 of the 255 patients assigned to low-dose warfarin. This finding was the equivalent of a 64 percent reduction in risk for those treated with warfarin. Results were similar for all patients — men and women and those of all ages — including those with factor V Leiden and the G20210A prothrombin polymorphism, common genetic variants that increase the risk of blood clots.

Major bleeding complications occurred in 2 patients in the placebo group and 5 in the low-dose warfarin group. There were 8 deaths in the placebo group compared to 4 in the low-dose warfarin group.

An analysis that combined the numbers of recurrent blood clots/cases of pulmonary embolism with the number of hemorrhages and deaths found a 48 percent reduction in risk for patients assigned to warfarin.

"This study gives us a new use for a 50-year-old drug," noted Ridker, who added that this is a very inexpensive therapy.

To interview NHLBI PREVENT project officer and study co-author Yves Rosenberg, M.D., contact the NHLBI Communications Office at 301-496-4236. To interview Dr. Ridker, please call Jeff Ventura at Brigham and Women's Hospital at 617-534-1600.

NHLBI is part of the National Institutes of Health (NIH), the Federal Government's primary agency for biomedical and behavioral research. NIH is a component of the U.S. Department of Health and Human Services. NHLBI press releases and other materials including information about high blood pressure, high blood cholesterol, and heart disease, are available online at www.nhlbi.nih.gov.

Last reviewed: 04 March 2004
Last updated: 14 October 2003
First published: 09 October 2003
Metadata| Permanence level: Permanent: Unchanging Content